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The efficacy of fluticasone furoate administered in the morning or evening is comparable in patients with persistent asthma

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ABSTRACT

Background: The inhaled corticosteroid fluticasone furoate (FF) is efficacious as a once-daily treatment for the management of asthma. Asthma is associated with circadian changes, with worsening lung function at night. We compared the efficacy of once-daily FF in the morning or evening for the treatment of asthma.

Methods: Adults with persistent bronchial asthma were enrolled into this randomised, repeat-dose, double-blind, double-dummy, placebo-controlled, three-way crossover study. After a 14-day run-in period, patients received either: FF 100 μg in the morning (AM); FF 100 μg in the evening (PM); or placebo, via the ELLIPTA® dry powder inhaler. Patients received all three treatments (14 ± 2 day duration) separated by a 14- to 21-day washout period. The primary endpoint was 24-h weighted mean forced expiratory volume in 1 s (FEV_1) measured at the end of each 14-day treatment.

Results: A total of 28 patients aged between 19 and 67 years were randomised and 21 (75%) completed all three study arms. Once-daily administration of FF 100 μg resulted in an increased 24-hour weighted mean FEV_1; differences between the adjusted means for AM and PM FF dosing versus placebo were 0.077 L (90% confidence interval [CI]: 0.001, 0.152) and 0.105 L (90% CI: 0.029, 0.180), respectively (adjusted mean difference: −0.028 L [90% CI: −0.102, 0.045]). AM or PM doses had comparable incidences of adverse events (AEs; 18/23 versus 18/24, respectively), no serious AEs occurred.

Conclusion: AM and PM doses of once-daily FF 100 μg produced comparable improvements in lung function relative to placebo.

1. Introduction

Asthma is a heterogeneous disease associated with airway inflammation, which has been estimated to affect over 240 million people worldwide [1]. Inhaled corticosteroids (ICS) are the mainstay of asthma treatment and are highly effective in reducing both asthma symptoms and the risk of asthma-related exacerbations, hospitalisations and death [2]. Although the importance of anti-inflammatory treatment is generally considered to be understood by patients with asthma, poor compliance with maintenance ICS treatment remains an issue and is associated with poor asthma-related outcomes [3]. For several ICS therapies, the frequency of administration is an important determinant of their efficacy and safety. Older ICS that necessitated administration up to four times daily have been largely superseded by twice-daily treatments, and are now increasingly being replaced by once-daily regimens. In an analysis of patient adherence to prescriptions in routine practice, once-daily ICS dosing was shown to improve adherence by approximately 20%, compared with twice-daily dosing [4]. However, it is important for a once-daily ICS to show similar efficacy and tolerability as the same dose given twice-daily.

Abbreviations: AE, adverse event; AM, morning; CI, confidence interval; FEV_1, forced expiratory volume in 1 s; FF, fluticasone furoate; FP, fluticasone propionate; ICS, inhaled corticosteroids; LABA, long-acting beta$_2$ agonist; PEF, peak expiratory flow; PM, evening; SABA, short-acting beta$_2$ agonist; SAE, serious adverse event; SD, standard deviation; URTI, upper respiratory tract infection.

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Fluticasone furoate (FF) is a new ICS that is structurally distinct from fluticasone propionate (FP) [5,6]. FF has greater glucocorticoid receptor binding affinity compared with other ICS [7], is highly retained in human lung tissue and has a more prolonged duration of anti-inflammatory activity than FP [8,9]. In clinical studies, once-daily inhaled FF was shown to be efficacious for pre-dose evening forced expiratory volume in 1 s (FEV_1) in patients with asthma [10–12], and was non-inferior to the same dose given twice-daily [13]. Inhaled FF monotherapy (100 μg and 200 μg; Arnuity ELLIPTA®) is now approved in a number of countries for once-daily treatment of asthma [14], as well as in combination with vilanterol (a new long-acting $beta_2$ agonist [LABA]), for the treatment of chronic obstructive pulmonary disease and asthma [15,16].

Circadian changes have been demonstrated in asthma, with lung function and symptoms worsening at night [17]. Sensitivity to the time of administration has been observed for some once-daily corticosteroids in asthma, where evening dosing has been associated with optimal efficacy and/or a reduction in cortisol-related adverse effects [18,19]. Morning (AM) and evening (PM) dosing schedules have been studied for a 400 μg dose of FF. Eight weeks of treatment with FF 400 μg administered once-daily PM via the DISKUS device or FF 200 μg administered twice-daily produced similar improvements in pre-dose (trough) FEV_1 [20]. In the same study, FF 400 μg once-daily in the morning was effective but resulted in a smaller improvement in pre-dose FEV_1 compared with FF 200 μg twice-daily or FF 400 μg once-daily PM administration. The effects of altering the time of day of dosing with FF at a clinically approved dose in asthma, delivered by the ELLIPTA dry powder inhaler, have not been specifically studied. Flexibility around the time of once-daily ICS administration to suit individual patient preferences is considered to be beneficial and may lead to improved adherence with prescribed treatment. This study was conducted to directly compare the efficacy of once-daily FF 100 μg administered either in the morning or evening in adult patients with asthma.

2. Patients and methods

2.1. Study oversight

The study (GSK study number: FFA117156; clinicaltrials.gov number: NCT01808339) was approved by the applicable institutional review board and independent ethics committee, and was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent. Study FFA117156 was conducted between March 2013 and March 2014 at the GSK Medicines Research Unit, New South Wales, Australia.

2.2. Study population

Men and women aged between 18 and 70 years were eligible to be enrolled. All patients had persistent bronchial asthma, with a pre-bronchodilator predicted FEV_1 of ≥60% at screening [21]. All patients were clinically stable on either low-to mid-dose ICS (for example FP 100–250 μg twice-daily [total daily dose 200–500 μg] or equivalent) with/without a short-acting $beta_2$ agonist (SABA) or a low-dose ICS/LABA combination (such as FP/salmeterol 100/50 μg twice daily, FP/salmeterol 125/25 μg twice daily, or equivalent) for at least four weeks preceding the screening visit. Patients demonstrated reversibility to salbutamol (albuterol) of ≥12% over baseline and an absolute change of ≥0.200 L within 60 min following four inhalations of albuterol/salbutamol aerosol (400 μg total dose). The 60-min period was chosen to allow the study site flexibility to measure reversibility. SABAs or LABAs were withheld for at least 6 or 24 h, respectively, prior to screening and study visits. Eligible patients were current non-smokers (pack history of ≤10 pack years), and had to be able to use the ELLIPTA inhaler satisfactorily.

Patients were excluded if they had a history of life-threatening asthma, any recent asthma exacerbation requiring oral corticosteroids (≤12 weeks prior to screening) or hospitalisation (≤6 months prior to screening), a history of hypersensitivity or suspected adverse reaction to components of the study medication, viral or bacterial infection of the upper or lower respiratory tract requiring antibiotics, or other diseases or contraindications that would put the patient at risk.

2.3. Study design

This single-centre study was carried out according to a randomised, repeat-dose, double-blind, double-dummy, placebo-controlled, three-way crossover design. Eligible patients entered a 14-day run-in period, during which time they discontinued all their usual asthma medications, with the exception of SABAs, which were used as rescue medication throughout the study.

During the run-in period patients recorded morning (approximately 09.00 h) and evening (approximately 21.00 h) peak expiratory flow (PEF) on diary cards using an electronic PEF meter. Run-in failures included patients who: resumed their normal asthma medication (other than albuterol/salbutamol), experienced a severe exacerbation (deterioration of asthma requiring the use of systemic corticosteroids), or developed oral or respiratory infections that led to a change in asthma management. To be eligible for randomisation, daily diary compliance was required for all AM and PM data on four or more of the last seven consecutive days of the run-in period.

At the end of the run-in period, eligible patients were randomly assigned to one of six sequences of three treatments delivered via the ELLIPTA inhaler. All inhalers used in this study were identical, and contained either FF or lactose (placebo). The 100 and 200 μg doses of FF are both approved as monotherapy for the treatment of persistent asthma in adults and adolescents in the USA. The FF 100 μg dose was selected for this study as it was considered likely that this would be the most frequently prescribed clinical dose.

Treatment regimens were: A) FF AM with placebo PM; B) placebo AM with FF PM; C) placebo AM and PM. AM and PM doses were administered at approximately 9:00 and 21:00 respectively. The treatment period durations were 14 ± 2 days, separated by 14- to 21-day washout periods. The final study day is referred to as 'Day 14', irrespective of the treatment period duration. Patients each received their three series of treatments according to one of the following sequences: ABC, ACB, BAC, BCA, CAB, CBA.

The first dose of each treatment was administered on Day 1 PM, and final doses on Day 14 PM and Day 15 AM. FEV_1 was measured every 3 h for 0–24 h at the end of each treatment period (i.e. from approximately 21:00 on Day 14 until 21:00 on Day 15). Patients attended the clinic during this 24-h period and the FEV_1 readings were supervised by clinic staff.

Protocol-defined stopping criteria for worsening asthma included one or more of the following: ≥4 consecutive days in which PEF (either AM, PM or both) fell below 80% of the mean AM PEF recorded during the last 7 days of the run-in period; ≥3 days in which ≥12 inhalations/day of albuterol/salbutamol were used; a severe asthma exacerbation (a deterioration requiring the use of systemic corticosteroids for ≥3 days, or an in-patient hospitalisation or emergency department visit that required systemic corticosteroids); or clinical asthma worsening, which required additional asthma treatment other than study medication or study supplied albuterol/salbutamol.

2.4. Study outcomes

The primary endpoint, 24-h weighted mean FEV_1 on Day 14, was analysed to estimate the effect of AM or PM dosing. Secondary endpoints included the effect of time of dosing on pre-treatment FEV_1 (measured on Day 14; AM and PM) and the safety (adverse events [AEs]) of AM or PM dosing.

2.5. Statistical analysis

Whilst no formal hypothesis testing was performed, differences between the three treatment regimens were compared using point estimates and corresponding 90% confidence intervals (CI), constructed for the difference between the adjusted mean of each test treatment and the adjusted mean of the reference treatment. Assuming a standard deviation (SD) of 0.16 L, an estimate based on historical data [22]; a sample size of 20 patients was required to have 90% power to detect a half-width difference of 0.085 L between AM, PM and placebo dosing for 24-h weighted-mean FEV_1 during Day 14. This calculation was based on a symmetric two-tailed procedure and a type I error rate of 10%.

Efficacy analyses were performed by fitting a mixed effects analysis of covariance model onto the 0–24 h weighted mean FEV_1. Fixed-effect terms were applied for treatments (AM, PM, or placebo). The treatment period, patient baseline FEV_1 (the mean measurement over the three treatment periods), period baseline FEV_1 (the difference between each treatment period's baseline measurement and the patient's baseline), gender and age were fitted as covariates; while the patient was fitted as a random effect. The difference between adjusted means and the corresponding two-sided 90% CI for AM minus placebo, PM minus placebo and AM minus PM were calculated.

2.6. Safety assessment

The incidence of all AEs (including treatment-related AEs, and serious AEs [SAEs]) was collected throughout the study.

3. Results

3.1. Patients

An overview of the patient disposition is shown in Fig. 1. Following the run-in period, 28 patients were randomised (safety/'all patients' population), of which 25 (89%) were included in the intent-to-treat population (defined as patients who had at least one baseline and one post-dose FEV_1 measurement). A total of 21 patients (75%) completed all three study arms. Seven patients failed to complete the study; five reached the protocol-defined stopping criteria (mainly asthma exacerbations), and two withdrew consent.

Demographic details and baseline lung function characteristics for the 'all patients' population are presented in Table 1. Patients were aged between 19 and 67 years at screening with a mean age of 31.7 years. Baseline mean pre-bronchodilator FEV_1 was 86.9% of predicted (range: 68.3–111.0%). All patients were required to demonstrate ≥12% responsiveness to albuterol/salbutamol, although one patient had a reversibility of 11.7%, which was rounded up to 12%, and the patient was included in the study. There were no significant protocol deviations that could have affected the study outcomes.

3.2. Primary endpoint: 0–24 h weighted mean FEV_1 on day 14

FF 100 μg administered either AM or PM for 14 days was associated with a similar increase in FEV_1, compared with placebo, at all time-points over the 0–24 h assessment period (Fig. 2). The treatment difference in weighted mean FEV_1, relative to placebo, was comparable for FF 100 μg whether it was dosed AM (0.077 L) or PM (0.105 L; Table 2). The difference between FF AM and FF PM adjusted means was −0.028 L (Table 2).

3.3. Secondary endpoint: pre-treatment FEV_1 (AM and PM) on day 14

There appeared to be no difference in pre-treatment FEV_1 between the AM and PM FF dosing regimens (Table 3). Compared with placebo, both FF 100 μg dosing regimens demonstrated higher pre-treatment FEV_1 values during Day 14, with differences in adjusted means ranging from 0.013 to 0.114 L (AM and PM, respectively).

3.4. Secondary endpoint: safety

There were no SAEs observed during this study. A total of 133 AEs were experienced by 26 patients; all AEs had resolved by the end of the study. AEs reported by ≥ 2 patients across all treatment groups are shown in Table 4, the most common of which were headache and upper respiratory tract infection (URTI). All AEs were assessed as mild or moderate in intensity, with the exception of one report of gastroenteritis that was severe, however this occurred seven days after placebo administration and was considered unrelated to treatment.

Five patients met the pre-defined lung function stopping criteria (four consecutive days when PEF [AM, PM or both] was <80% of the individual's baseline value) and were withdrawn from the study. At withdrawal, four of the patients were receiving placebo and one was receiving FF 100 μg PM dosing.

There were no obvious differences in the number of AE episodes reported after AM or PM dosing. URTIs (viral and non-viral) were reported by 15 patients (54%).

4. Discussion

This crossover study was conducted to investigate the effect of the time of dosing, either in the morning or in the evening, on the efficacy of once-daily FF 100 μg in patients with persistent bronchial asthma. FEV_1 was recorded at regular 3-h intervals 0–24 h after dosing on Day 14. FEV_1 was stable over this entire 24-h period, with similar FEV_1 profiles following AM or PM administration of FF 100 μg. Both morning and evening dosing with FF 100 μg produced comparable increases in weighted mean FEV_1 (0–24 h at the end of the 14-day treatment period, the primary endpoint), with a mean difference between AM and PM administration of −0.028 L (90% CI: −0.102, 0.045). The difference from placebo was slightly lower for morning administration (0.077 L; 90% CI: 0.001 L, 0.152 L), compared with evening dosing (0.105 L; 90% CI: 0.029 L, 0.180 L). Other studies have also demonstrated that morning and evening doses of ICS are equally efficacious. For example, FF/vilanterol had comparable trough FEV_1 on Day 14 after morning and evening dosing [22] and mometasone furoate produced comparable changes in symptom scores after morning and evening dosing [23].

Our study also included assessment of morning and evening trough FEV_1 as a secondary endpoint, as this parameter is frequently used in larger clinical trials. On Day 14, morning and evening trough FEV_1 values were greater following AM or PM FF 100 μg, compared with placebo, with minor differences between the AM and PM regimens supporting comparable efficacy of FF regardless of the timing of administration. The differences from placebo were slightly less than those seen in large phase III trials. For example, in a large, six-month, parallel group, phase III clinical trial in patients with asthma, the mean difference from placebo in

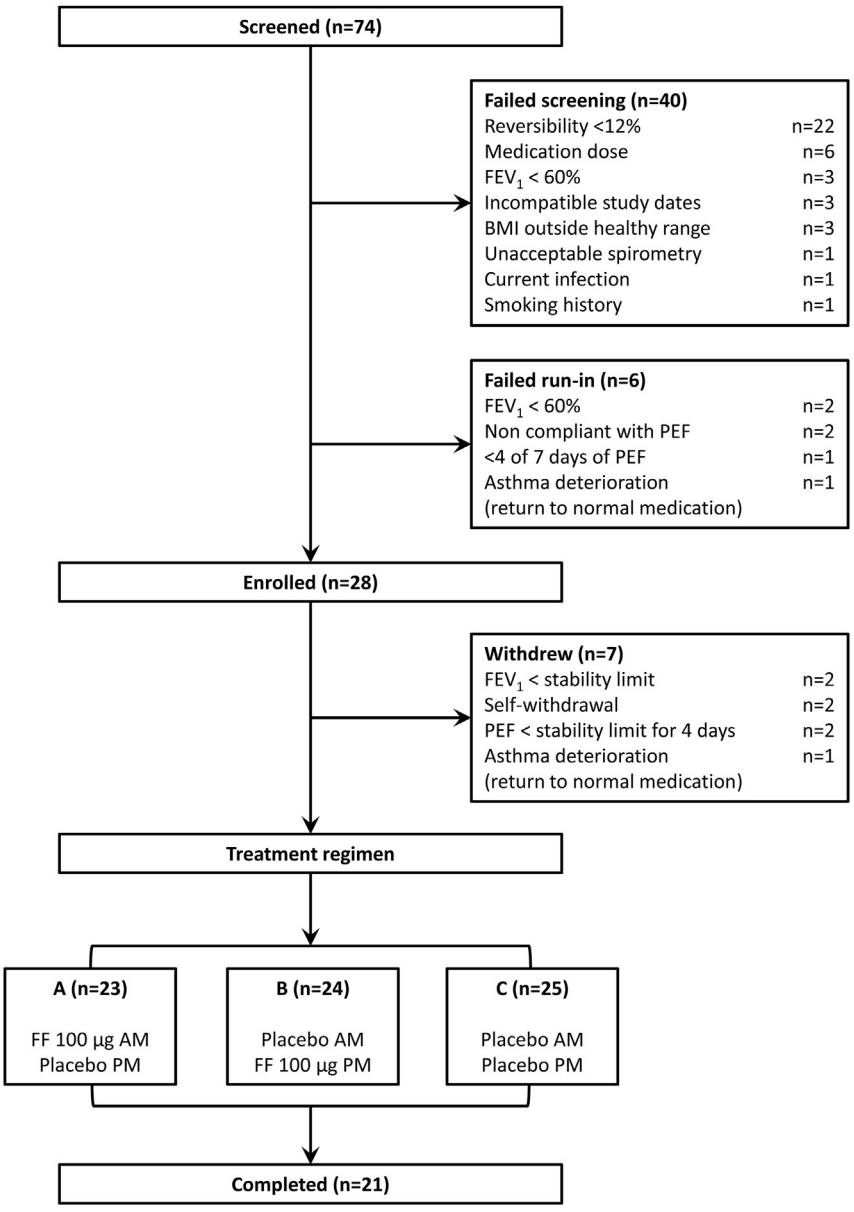

Fig. 1. Patient disposition.
FEV_1, forced expiratory volume in 1 s; BMI, body mass index; PEF, peak expiratory flow; FF, fluticasone furoate; AM, morning dose (approximately 09.00 h); PM, evening dose (approximately 21.00 h).

evening trough FEV_1 with FF 100 µg (evening dosing) was 0.146 L (95% CI: 0.036 L, 0.257 L) at 24 weeks [24]. In a 12-week phase III study, the difference between FF 100 µg and placebo (evening dosing) was 0.136 L (95% CI: 0.051 L, 0.222 L) [25]. The 0.114 L mean difference from placebo in evening trough FEV_1, with FF 100 µg evening dosing observed in our study was within the 95% CIs for the same comparison in the 12-week phase III study. Patients in our study had less severe asthma compared with the patients in the 12-week phase III study (with 87% mean predicted pre-bronchodilator FEV_1 and mean baseline FEV_1 of 3.087 L, compared with 70.49% [± 11.01% L SD] mean predicted pre-bronchodilator FEV_1 and baseline FEV_1 of 2.290 L [± 0.617 L SD]) [25]. In our study, patients also showed lower mean baseline FEV_1 reversibility to salbutamol than the 12-week phase III study patients (18%, compared with 30.66% [± 19.74% SD], respectively) [25]. These differences in underlying asthma severity are considered to be the most likely reason for the lower trough FEV_1 response to FF 100 µg seen in the present study.

Although established ICS are typically administered twice-daily, studies comparing their efficacy (in terms of pre-dose FEV_1) when administered once-daily in the morning or evening in patients with asthma have shown that evening dosing is as effective or is more effective than morning dosing [18,26]. At a daily dose level above the approved therapeutic range, FF 400 µg once-daily in the evening produced similar efficacy (pre-dose FEV_1) to 200 µg twice-daily, although a lesser effect was seen with FF 400 µg once-daily in the morning [20]. By contrast, an early study with FF 100 µg administered by a different dry powder inhaler (Rotadisk® Diskhaler) to that used in the present study (ELLIPTA) showed similar efficacy between morning and evening dosing [27]. The results of the present study are comparable with the results obtained by Medley et al. [27]; both studies were conducted at the same clinical dose.

In addition to circadian variations in lung function and airway responsiveness, the circadian rhythm in serum cortisol has been well characterised, with peak concentrations in the early morning

Table 1
Patient demographics and lung function at screening.

Characteristic	Value
Mean age, years (range)	31.7 (19–67)
Gender, female/male, n (%)	15 (54)/13 (46)
Race, n (%)	
White	21 (75)
Mixed Race	3 (11)
Asian	3 (11)
African Heritage	1 (4)
Mean pre-bronchodilator FEV_1, L (SD)	3.087 (0.693)
Mean post-bronchodilator FEV_1, L (SD)	3.641 (0.775)
Pre-bronchodilator FEV_1% predicted, mean (range)	86.9 (68.3–111)
Post-bronchodilator FEV_1% predicted, mean (range)	102 (87.5–127)
% reversibility, mean (range)	18.0 (11.7[a]–40.2)

FEV_1, forced expiratory volume in 1 s; SD, standard deviation.
[a] One patient demonstrated reversibility of 11.7% and continued on the study.

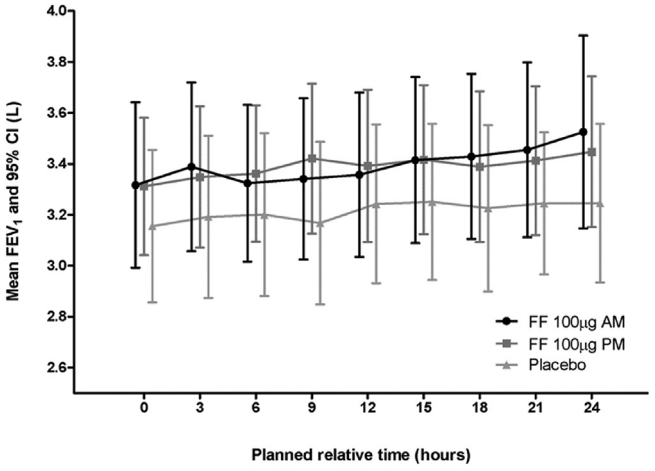

Fig. 2. FEV_1 over a 24-h period on Day 14, following administration of FF 100 μg AM or PM and placebo for 14 days in patients with asthma (n = 28). AM, morning dose (approximately 09.00 h); CI, confidence interval; FEV_1, forced expiratory volume in 1 s; FF, fluticasone furoate; PM, evening dose (approximately 21.00 h).

and trough concentrations at night. A greater effect of ICS on cortisol has been reported with morning dosing compared with evening dosing, indicating that evening dosing with ICS may be optimal [19,28]. However, the pharmacokinetic-pharmacodynamic relationship for the effects of FF on serum and urinary cortisol has been extensively studied and clearly demonstrates that FF systemic exposure at clinical doses is not associated with significant cortisol suppression [29]. In clinical studies in patients with persistent asthma, FF doses <800 μg were not associated with urinary cortisol suppression [11], with no effect on serum or urinary cortisol seen after administration of clinical doses of FF 100 μg and 200 μg (administered with vilanterol 25 μg) for 6 weeks [30]. Although an effect of AM or PM dosing on cortisol has not been studied, based on these data, an effect of FF 100 μg (dosed in either the morning and evening) on serum or urinary cortisol was considered unlikely.

Dosing with FF 100 μg in the morning or evening for 14 days was well tolerated in the patients with asthma participating in this study. There were no obvious differences in the number of AEs reported after morning or evening dosing and no SAEs were reported during the study. In addition, all AEs following treatment with FF were mild or moderate in intensity. Five patients were withdrawn for meeting pre-defined lung function stopping criteria; four of these were receiving placebo at the time of withdrawal. The incidence of URTIs (viral and non-viral) was comparable after AM and PM dosing, similarly no difference in AE incidence was seen in a larger clinical trial comparing FF morning or evening dosing with placebo [27].

A key strength of this study is that lung function was thoroughly assessed at regular intervals over 24 h to determine the effects of FF 100 μg (AM or PM dosing). A limitation of the study is that the two-week treatment period could be considered insufficient to characterise the long-term clinical efficacy of an ICS. However, while a further progressive improvement in lung function has been seen with long-term ICS treatment, the majority of the beneficial effects of FF 100 μg were apparent after dosing for two weeks, with relatively minor further improvements seen with treatment up to 26 weeks [31]. A further potential limitation of the study is that while the sample size was sufficient to provide an indication of the effect of dosing time on the efficacy of FF 100 μg in asthma, a much larger study would be required to make confirmatory claims regarding

Table 2
Statistical analysis of the weighted mean FEV_1 (0–24 h) (L) on Day 14 following administration of FF 100 μg (AM or PM) and placebo for 14 days.

Comparison	Adjusted means		Difference in adjusted means	90% CI of the difference
	Test	Reference		
FF 100 μg AM versus placebo	3.303	3.227	0.077	(0.001, 0.152)
FF 100 μg PM versus placebo	3.332	3.227	0.105	(0.029, 0.180)
FF 100 μg AM versus FF 100 μg PM	3.303	3.332	−0.028	(−0.102, 0.045)

AM, morning dose (approximately 09.00 h); CI, confidence interval; FEV_1, forced expiratory volume in 1 s; FF, fluticasone furoate; PM, evening dose (approximately 21.00 h).

Table 3
Statistical analysis of the pre-treatment FEV_1 (L) on Day 14 following administration of FF 100 μg (AM or PM) and placebo for 14 days.

	Comparison	Adjusted means		Difference in adjusted means	90% CI of the difference
		Test	Reference		
AM pre-treatment FEV_1	FF 100 μg AM versus placebo	3.299	3.286	0.013	(−0.067, 0.093)
	FF 100 μg PM versus placebo	3.359	3.286	0.073	(−0.007, 0.153)
	FF 100 μg AM versus FF 100 μg PM	3.299	3.359	−0.060	(−0.137, 0.018)
PM pre-treatment FEV_1	FF 100 μg AM versus placebo	3.236	3.177	0.059	(−0.041, 0.160)
	FF 100 μg PM versus placebo	3.290	3.177	0.114	(0.013, 0.214)
	FF 100 μg AM versus FF 100 μg PM	3.236	3.290	−0.054	(−0.152, 0.044)

AM, morning dose (approximately 09.00 h); CI, confidence interval; FEV_1, forced expiratory volume in 1 s; FF, fluticasone furoate; PM, evening dose (approximately 21.00 h).

Table 4
Adverse events reported by ≥ 2 patients across all treatment groups, following administration of FF 100 μg (AM or PM) and placebo for 14 days.

N (%)	Placebo (n = 25)	FF 100 μg AM (n = 23)	FF 100 μg PM (n = 24)	Total (n = 28)
Any event	16 (64)	18 (78)	18 (75)	26 (93)
Headache	9 (36)	12 (52)	10 (42)	18 (64)
URTI	2 (8)	6 (26)	1 (4)	7 (25)
Viral URTI	2 (8)	1 (4)	5 (21)	8 (29)
Nasopharyngitis	1 (4)	2 (9)	1 (4)	4 (14)
Gastroenteritis	3[a] (12)	1 (4)	0	3 (11)
Nausea	1 (4)	1 (4)	2 (8)	2 (7)
Vomiting	1 (4)	0	1 (4)	2 (7)
Eczema	2 (8)	1 (4)	0	3 (11)
Dysmenorrhoea	2 (8)	1 (4)	2 (8)	4 (14)
Seasonal allergy	0	1 (4)	1 (4)	2 (7)

AM, morning dose (approximately 09.00 h); FF, fluticasone furoate; URTI, upper respiratory tract infection; PM, evening dose (approximately 21.00 h).
[a] Including one case of viral gastroenteritis.

equivalence of morning and evening dosing with FF. However, the similar weighted mean FEV_1 for morning and evening dosing with FF 100 μg and comparable efficacy to that seen in larger clinical studies with FF 100 μg suggests that similar efficacy would be anticipated with morning or evening dosing with FF.

5. Conclusions

Once-daily administration of FF 100 μg for 14 days resulted in an increased 0–24 h weighted mean FEV_1, compared with placebo, with no appreciable difference between morning or evening dosing. Increases in trough FEV_1 (AM or PM) were also comparable between morning and evening dosing. There were no apparent differences in the overall incidence of AEs following FF 100 μg dosing in either the morning or evening.

6. Author contributions

RDK, JB, JR, RR and PST contributed to the conception and design of these analyses and were involved in the interpretation of the data; PST was involved in the data acquisition; AB was also involved in the interpretation of the data. All authors wrote the manuscript.

Conflict of interest statement

RDK, JB, AB, JR and RR are employees of GSK and hold stocks in GSK, PST has acted as a consultant and investigator for GSK.

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